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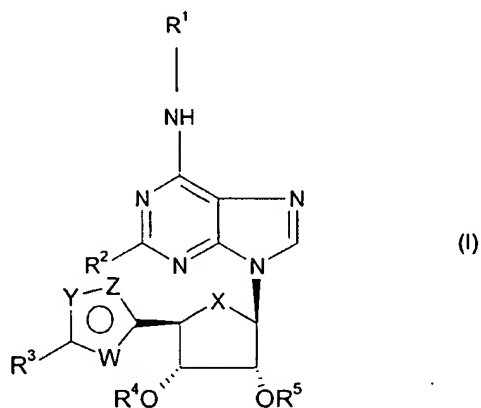
(54) Title: **FORMULATIONS OF ADENOSINE A1 AGONISTS**

(57) Abstract: The present invention provides a method of treating conditions associated with pain and alleviating the symptoms associated therewith which comprises administering to a mammal, including man, an adenosine A1 agonist or a physiologically acceptable salt or solvate thereof and an NSAID, e.g. a COX-2 inhibitor, or a physiologically acceptable salt or solvate thereof. The present invention also provides pharmaceutical formulations and patient packs comprising said combinations.

### Formulations of Adenosine A1 agonists

The present invention relates to the treatment of conditions associated with pain including acute pain, chronic pain, inflammatory pain, neuropathic pain and pain associated with migraine, tension headaches, cluster headaches and functional bowel disorder. In particular it relates to the use of an adenosine A1 agonist in conjunction with a non-steroidal anti-inflammatory drug (NSAID), e.g. COX-2 inhibitor.

A variety of compounds which are agonists at the adenosine A1 receptor have been described in the art. These include compounds described in published patent applications WO99/24449, WO99/24450, WO99/24451, WO97/43300, WO98/16539, WO98/04126, WO98/01459, EP0322242, GB2226027, EP222330, WO98/08855, WO94/0707 and WO99/67262 which are incorporated herein by reference. WO99/67262 discloses compounds of formula (I) which are agonists at the adenosine A1 receptor



wherein X represents O or CH<sub>2</sub>;

R<sup>2</sup> represents C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy, halogen or hydrogen;

R<sup>3</sup> represents H, phenyl (optionally substituted by halogen), a 5 or 6 membered heteroaryl group, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylO(CH<sub>2</sub>)<sub>n</sub> where n is 0-6, C<sub>3-7</sub> cycloalkyl,

C<sub>1-6</sub> hydroxyalkyl, halogen or a C<sub>1-6</sub> straight or branched alkyl, C<sub>1-6</sub> alkenyl or C<sub>1-6</sub> alkynyl group optionally substituted by one or more halogens.

Y and Z represent O, N, CH, N(C<sub>1-6</sub> alkyl)

5 W represents CH, O, N, S, N(C<sub>1-6</sub> alkyl)

and wherein at least one of W and Z represents a heteroatom (and when Y, Z and/or W is N, the presence or absence of an additional H would be apparent to a person skilled in the art)

10 with the proviso that when W represents CH, Z represents N and Y represents O, R<sup>3</sup> cannot be H.

R<sup>4</sup> and R<sup>5</sup> independently represent H or a C<sub>1-6</sub> straight chain or branched alkyl group.

15 R<sup>1</sup> represents hydrogen or a group selected from

(1) -(alk)<sub>n</sub> – (C<sub>3-7</sub>) cycloalkyl, including bridged cycloalkyl, said cycloalkyl group optionally substituted by one or more substituents selected from OH, halogen, - (C<sub>1-3</sub>) alkoxy, wherein (alk) represents C<sub>1-3</sub> alkylene and n represents 0 or 1.

20 (2) an aliphatic heterocyclic group of 4 to 6 membered rings containing at least one heteroatom selected from O, N or S, optionally substituted by one or more substituents selected from the group consisting of -(C<sub>1-3</sub>)alkyl, -CO<sub>2</sub>-(C<sub>1-4</sub>)alkyl, -CO(C<sub>1-3</sub>alkyl), -S(=O)<sub>n</sub>-(C<sub>1-3</sub>alkyl), -CONR<sup>a</sup>R<sup>b</sup> (wherein R<sup>a</sup> and R<sup>b</sup> independently represent H or C<sub>1-3</sub>alkyl) or =O; where there is a sulfur atom in the heterocyclic  
25 ring, said sulfur is optionally substituted by (=O)<sub>n</sub>, where n is 1 or 2.

(3) Straight or branched C<sub>1-12</sub> alkyl, optionally including one or more O, S(=O)<sub>n</sub> (where n is 0, 1 or 2) and N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups, phenyl, halogen, hydroxy, C<sub>3-7</sub> cycloalkyl or NR<sup>a</sup>R<sup>b</sup> wherein R<sup>a</sup> and R<sup>b</sup> independently represent  
30 hydrogen, C<sub>3-7</sub> cycloalkyl or a C<sub>1-6</sub> straight chain or branched alkyl optionally substituted by C<sub>3-7</sub> cycloalkyl;

(4) a fused bicyclic aromatic ring



wherein B represents a 5 or 6 membered heterocyclic aromatic group containing 1 or more O, N or S atoms, wherein the bicyclic ring is attached to the nitrogen atom of formula (I) via a ring atom of ring A and ring B is optionally substituted by  $-\text{CO}_2-(\text{C}_{1-3}\text{alkyl})$ .

- (5) a phenyl group optionally substituted by one or more substituents selected from:
- halogen,  $-\text{SO}_3\text{H}$ ,  $-(\text{alk})_n\text{OH}$ ,  $-(\text{alk})_n-\text{cyano}$ ,  $-(\text{O})_n-(\text{C}_{1-6})\text{alkyl}$  (optionally substituted by one or more halogens),  $-(\text{alk})_n-\text{nitro}$ ,  $-(\text{O})_m-(\text{alk})_n-\text{CO}_2\text{R}^c$ ,  $-(\text{alk})_n-\text{CONR}^c\text{R}^d$ ,  $-(\text{alk})_n-\text{COR}^c$ ,  $-(\text{alk})_n-\text{SOR}^e$ ,  $-(\text{alk})_n-\text{SO}_2\text{R}^e$ ,  $-(\text{alk})_n-\text{SO}_2\text{NR}^c\text{R}^d$ ,  $-(\text{alk})_n\text{OR}^c$ ,  $-(\text{alk})_n-(\text{CO})_m-\text{NHSO}_2\text{R}^e$ ,  $-(\text{alk})_n-\text{NHCOR}^c$ ,  $-(\text{alk})_n-\text{NR}^c\text{R}^d$  wherein m and n are 0 or 1 and alk represents a  $\text{C}_{1-6}$ alkylene group or  $\text{C}_{2-6}$  alkenyl group.

- (6) A phenyl group substituted by a 5 or 6 membered heterocyclic aromatic group, said heterocyclic aromatic group optionally being substituted by  $\text{C}_{1-3}\text{alkyl}$  or  $\text{NR}^c\text{R}^d$ .

$\text{R}^c$  and  $\text{R}^d$  may each independently represent hydrogen, or  $\text{C}_{1-3}$  alkyl or when part of a group  $\text{NR}^c\text{R}^d$ ,  $\text{R}^c$  and  $\text{R}^d$  together with the nitrogen atom may form a 5 or 6 membered heterocyclic ring optionally containing other heteroatoms, which heterocyclic ring may optionally be substituted further by one or more  $\text{C}_{1-3}$  alkyl groups.

$\text{R}^e$  represents  $\text{C}_{1-3}\text{alkyl}$

and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof.

- These compounds are described as being useful in the treatment of pain, cardiac disorders, CV disorders including hyperlipidemia, diabetes, sleep apnoea, CNS disorders including epilepsy. The above applications also describe in relation to the adenosine A1 agonists they disclose both suitable methods for their preparation and doses for their administration.

We have now found that administration of an adenosine A1 agonist in conjunction with an NSAID, e.g. COX-2 inhibitor, is beneficial in the treatment of conditions associated with pain and in alleviating the symptoms associated therewith.

The use of combinations of the present invention may give rise to an equivalent effect in the treatment of conditions associated with pain and in alleviating the symptoms associated therewith, or an increase in drug efficacy because synergy between compounds occurs. The use of combinations of the present invention may alternatively and/or additionally reduce side effects compared to administration of a single compound. Drug efficacy may be assessed using pain models such as carrageenan model (Guilbaud G. & Kayser V. Pain 28 (1987) 99-107) for acute inflammatory pain, FCA model (Freund's Complete Adjuvant) (Hay et al., Neuroscience Vol 78, No 3 pp843-850, 1997) for chronic inflammatory pain, or CCI model (Chronic Constriction Injury) (Bennett, G. J. & Xie. Y.K. (1988) Pain, 33: 87-107) for neuropathic pain.

According to one aspect of the invention we therefore provide a method of treating conditions associated with pain and alleviating the symptoms associated therewith which comprises administering to a mammal, including man, an adenosine A1 agonist or a pharmaceutically acceptable derivative thereof and an NSAID, e.g. COX-2 inhibitor, or a pharmaceutically acceptable derivative thereof.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.

According to another aspect of the invention we provide the use of an adenosine A1 agonist or a pharmaceutically acceptable derivative thereof and an NSAID, e.g. COX-2 inhibitor, or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of conditions associated with pain and the alleviation of symptoms associated thereof.

The combinations of the invention are useful as analgesics. They are therefore useful in treating or preventing pain. They may be used to improve the condition of a host, typically of a human being, suffering from pain. They may be employed to alleviate pain in a host. Thus, the combinations of the invention may be used as a preemptive analgesic to treat acute pain such as musculoskeletal pain, post operative pain and surgical pain, chronic pain such as chronic inflammatory pain (e.g. rheumatoid arthritis (RA) and osteoarthritis (OA), neuropathic pain (e.g. post herpetic neuralgia (PHN), trigeminal neuralgia, neuropathies associated with diabetes and sympathetically maintained pain) and pain associated with cancer and fibromyalgia. The combinations of the invention may also be used in the treatment or prevention of migraine and/or pain associated with migraine, tension headache and cluster headaches and pain associated with Functional Bowel Disorders (e.g. Irritable Bowel Syndrome), non cardiac chest pain and non ulcer dyspepsia.

Additionally, the combinations of the present invention exhibit analgesic and anti-inflammatory activity and are therefore useful in a number of chronic inflammatory pain conditions such as OA, RA and neuropathic conditions such as fibromyalgia and PHN.

By pharmaceutically acceptable derivative is meant any pharmaceutically acceptable salt, solvate, ester or amide, or salt or solvate of such ester or amide, of the adenosine A1 agonist or NSAID, e.g. COX-2 inhibitor, or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) the adenosine A1 agonist or NSAID, e.g. COX-2 inhibitor, or an active metabolite or residue thereof.

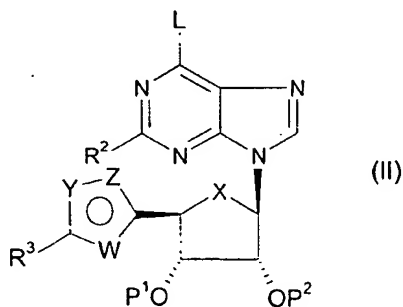
Suitable physiologically acceptable salts according to the invention include acid addition salts formed with inorganic acids such as hydrochlorides, hydrobromides, phosphates and sulphates and with organic acids, for example tetrates, maleates, fumarates, succinates and sulphonates.

Suitable adenosine A1 agonists include adenosine, (2S, 3S, 4R, 5R)-2-(5 tert-butyl-[1,3,4]oxadiazol-2-yl)-S-[6-(4-chloro-2-fluoro-phenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol (synthesis as in Example 1), N-[1S, trans)-2-

hydroxycyclopentyl]adenosine and N-(4-chloro-2-fluoro-phenyl)-5'-O-trifluoromethyl-adenosine. Particularly preferred are N-(4-Chloro-2-fluoro-phenyl)-5'-O-trifluoromethyl-adenosine and (2S, 3S, 4R, 5R)-2-(5 tert-butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluoro-phenylamino)-purin-9-yl]-tetrahydrofuran-3,4-diol.

The compounds of WO99/67262 and physiologically acceptable salts or solvates thereof may be prepared by the processes described below. In the following description, the groups  $R^1$ ,  $R^2$  and  $R^3$  are as defined for compounds of formula (I) unless otherwise stated.

According to a first general process A, a compound of formula (I) may be prepared by reacting a compound of formula (II)



wherein L represents a leaving group such as a halogen atom (e.g. chlorine), or a linker group capable of binding to a solid phase polymeric support (e.g. a polystyrene resin) and for example may be  $-\text{SO}_2\text{C}_{1-4}\text{alkylene}$  and  $P^1$  and  $P^2$  represent hydrogen,  $\text{C}_{1-6}$  straight chain or branched alkyl or a suitable protecting group (e.g. acetyl or a protecting group wherein  $P^1$  and  $P^2$  together form an alkylidene group) with a compound of formula  $\text{R}^1\text{NH}_2$  or a salt thereof under basic conditions. The 4'-heterocycle group substituent may be protected if required.

Compounds of formula (II) may be used to produce compounds of formula (I) directly by reaction with the group  $\text{R}^1\text{NH}_2$  either in the absence or presence of a solvent such as an alcohol (e.g. a lower alkanol such as isopropanol, t-butanol or 3-pentanol), an ether (e.g. tetrahydrofuran or dioxan), a substituted amide (e.g. dimethylformamide), a halogenated hydrocarbon (e.g. chloroform), an aromatic

hydrocarbon (e.g. toluene), dimethyl sulfoxide (DMSO) or acetonitrile, preferably at an elevated temperature (e.g. up to the reflux temperature of the solvent), in the presence of a suitable acid scavenger, for example, inorganic bases such as sodium, cesium or potassium carbonate, or organic bases such as triethylamine, diisopropylethylamine or pyridine, optionally in the presence of a palladium catalyst (e.g. palladium acetate) and phosphine ligand (e.g. R-(+)-2,2'-bis(diphenylphosphino)-1-1' binaphthyl).

Optionally, where at least one of Y, Z and W is N, alkylation may be carried out on a N atom at Y, Z or W at any appropriate stage in the synthesis.

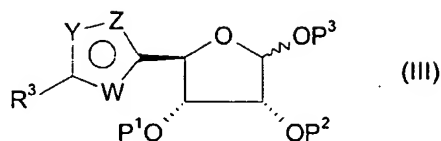
The above reactions may be preceded or followed where appropriate by in situ removal of the P<sup>1</sup> and P<sup>2</sup> protecting groups. For example when P<sup>1</sup> and P<sup>2</sup> represent acetyl, this may be effected with an amine such as ammonia or tert-butylamine in a solvent such as methanol or when P<sup>1</sup> and P<sup>2</sup> represent an alkylidene by acid hydrolysis, e.g. with trifluoroacetic acid (TFA). Interconversion of P<sup>1</sup> and P<sup>2</sup> protecting groups may occur at any stage in the preparation of the compounds of formula (II), for example when P<sup>1</sup> and P<sup>2</sup> represent acetyl, compounds of formula (II) may be prepared from compounds wherein P<sup>1</sup> and P<sup>2</sup> together represent an alkylidene protecting group by acid catalysed removal of the alkylidene protecting group, e.g. with hydrogen chloride in methanol followed by in situ acylation, for example with acetic anhydride in the presence of a base such as pyridine, in a solvent such as dichloromethane.

Otherwise, interconversion of P<sup>1</sup> and P<sup>2</sup> protecting groups may occur at any stage during the preparation of compounds of formula (II).

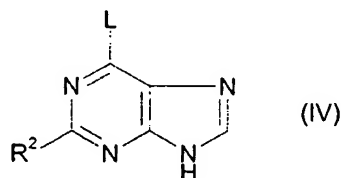
It will be apparent to persons skilled in the art that in the preparation of compounds of formula (II) or (I) the 4'-heterocycle may be formed at any stage. For example, heterocycles may be prepared from carboxylic acid or acetylene starting materials before the addition of the purine ring (see Schemes 1, 1a and 2) or heterocycles may be formed after the addition of the purine ring (see Scheme 3).



Compounds of formula (II) where  $X = O$  may be prepared by reacting compounds of formula (III)



wherein  $P^3$  represents a suitable protecting group, for example acetyl, or a substituent such as  $C_{1-3}$  alkyl, and  $P^1$ ,  $P^2$  and  $R^3$  are as defined above, with compounds of formula (IV)



wherein  $L$  and  $R^2$  are as defined above.

The reaction is conveniently carried out in a suitable solvent, such as acetonitrile in the presence of a silylating agent such as trimethylsilyl trifluoromethane sulfonate and a base such as diazabicyclo[5.4.0]undec-7-ene (DBU). Alternatively the compound of formula (IV) may first be silylated with a suitable silylating agent e.g. hexamethyldisilazane followed by reaction of the silylated intermediate with a compound of formula (III) and a suitable Lewis acid, e.g. trimethylsilyl trifluoromethanesulfonate in a suitable solvent such as acetonitrile.

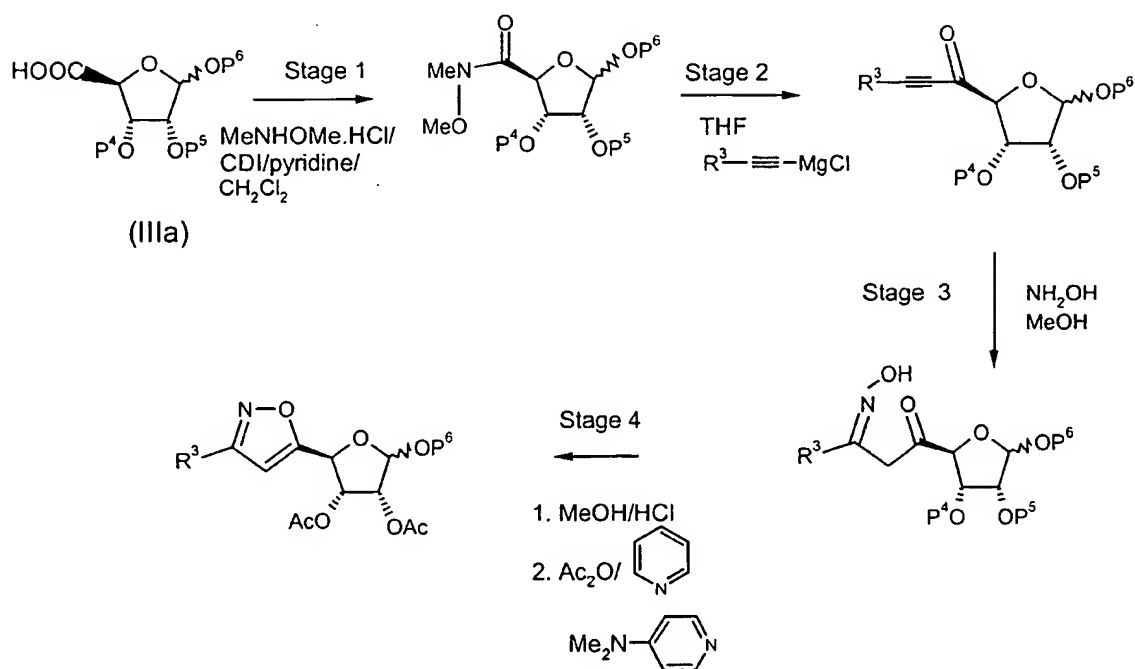
Compounds of formula (IV) are either known in the art or may be prepared from known compounds using methods analogous to those used to prepare the known compounds of formula (IV).

As described above, the compounds of formula (III) may be prepared from alternative protected compounds by replacement of the alternate  $P^1$  and  $P^2$  protecting groups with other  $P^1$  and  $P^2$  groups. These represent an exchanging

of one protecting group for another and will be apparent to those skilled in the art. Compounds of formula (III) may be made for example by the following syntheses:

- 5 Compounds of formula (III) may be prepared, for example when the heterocycle defined by W, Y and Z hereinabove represents an isoxazole (optionally substituted) by the following reaction schemes.

**Scheme 1**



10

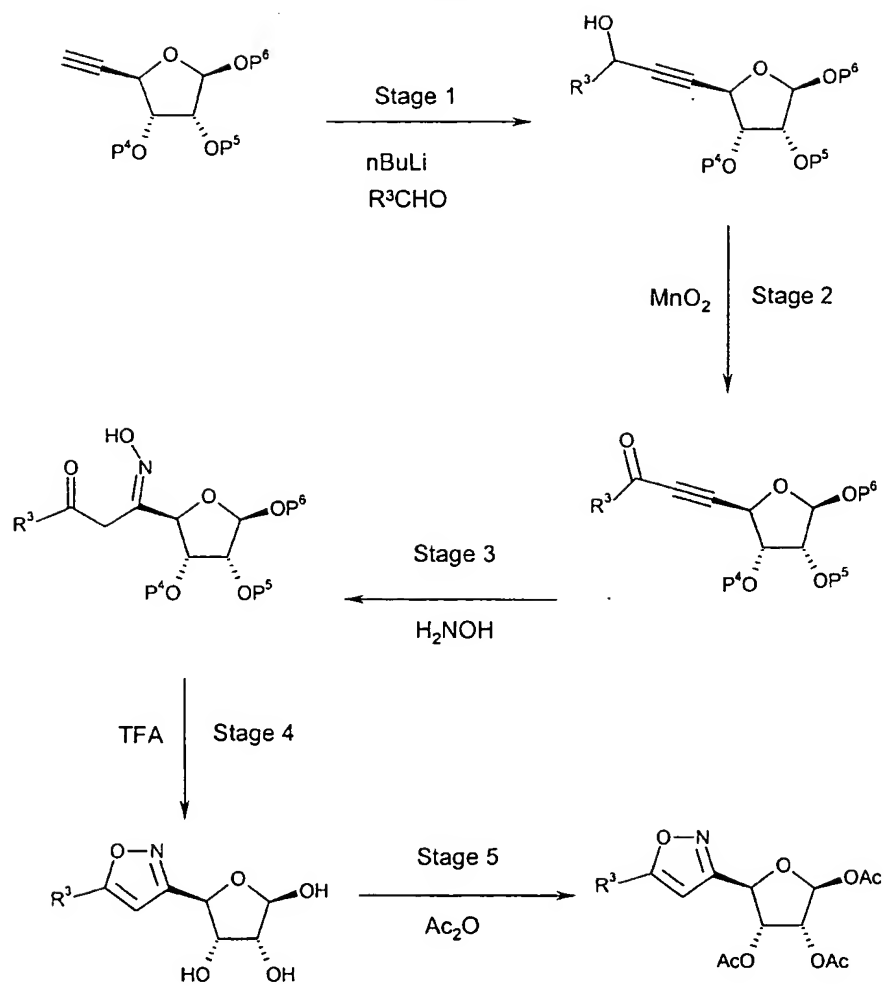
General conditions for Stages 1-4 will be known to persons skilled in the art. It will also be appreciated that the reagents and conditions set out in Scheme 1 are example conditions and alternative reagents and conditions for achieving the same chemical transformation may be known to persons skilled in the art.  $\text{P}^4$  and  $\text{P}^5$  together represent alkylidene protecting group(s).  $\text{P}^6$  represents  $\text{C}_{1-4}$  alkyl.  $\text{R}^3$  is as previously defined.

15

Although scheme 1 shows the preparation of compounds of formula (III) where the heterocycle moiety is an isoxazole it would be apparent to a person skilled in the art that other standard methods could be employed to produce compounds of formula (III) with other heterocycles from carboxylic acid starting materials.

5

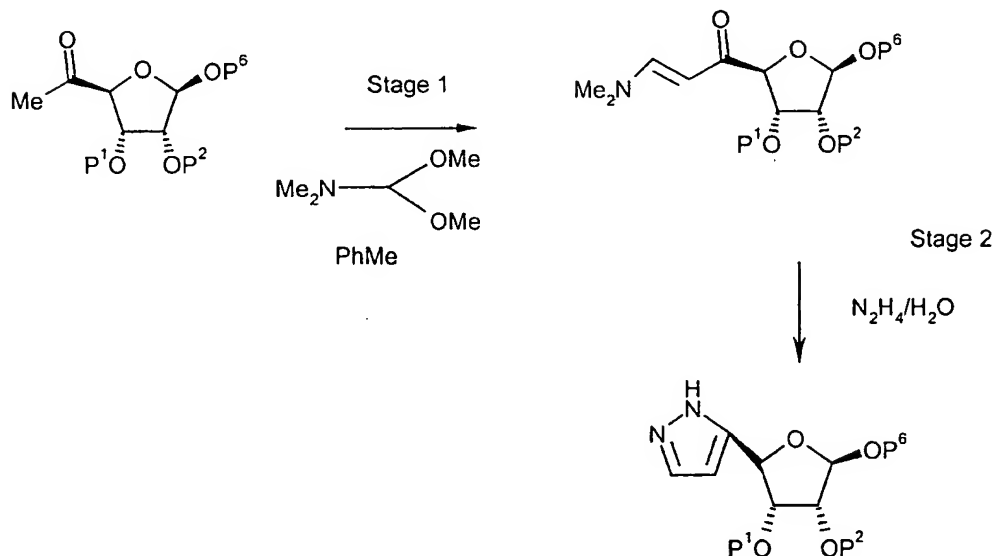
An alternative method for synthesis of compounds of formula (III) is shown in Scheme 1a.

**Scheme 1a**

General conditions for Stages 1-5 in Scheme 1a will be known to persons skilled in the art.  $R^3$ ,  $P^4$ ,  $P^5$  and  $P^6$  are as previously defined.

5 Scheme 2 represents a method of preparing compounds of formula (III) when  $Y = N$ ,  $Z = NH$ ,  $W = CH$  and  $R^3 = H$  or tautomers thereof.  $P^1$ ,  $P^2$  and  $P^6$  are as previously defined.

**Scheme 2**



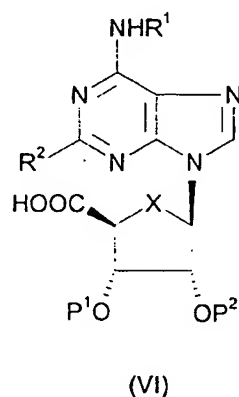
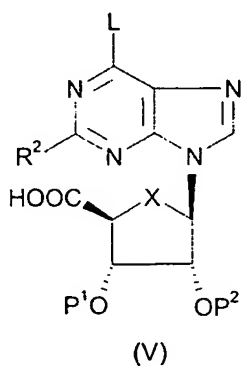
10 A further process (B) comprises converting a compound of formula (I) into a different compound of formula (I) by modifying the  $R^1$ ,  $R^2$  and/or  $R^3$  groups therein.

15 Compounds of the formula  $R^1NH_2$  are either known compounds or may be prepared from known compounds using conventional procedures.

Specific optical isomers of a compound of formula (I) may be obtained by conventional methods for example, by synthesis from an appropriate asymmetric starting material using any of the processes described herein, or where

appropriate by separation of a mixture of isomers of a compound of formula (I) by conventional means e.g by fractional crystallisation or chromatography.

According to a third process (C), compounds of formula (I) may be prepared from compounds of formula (V) or (VI):

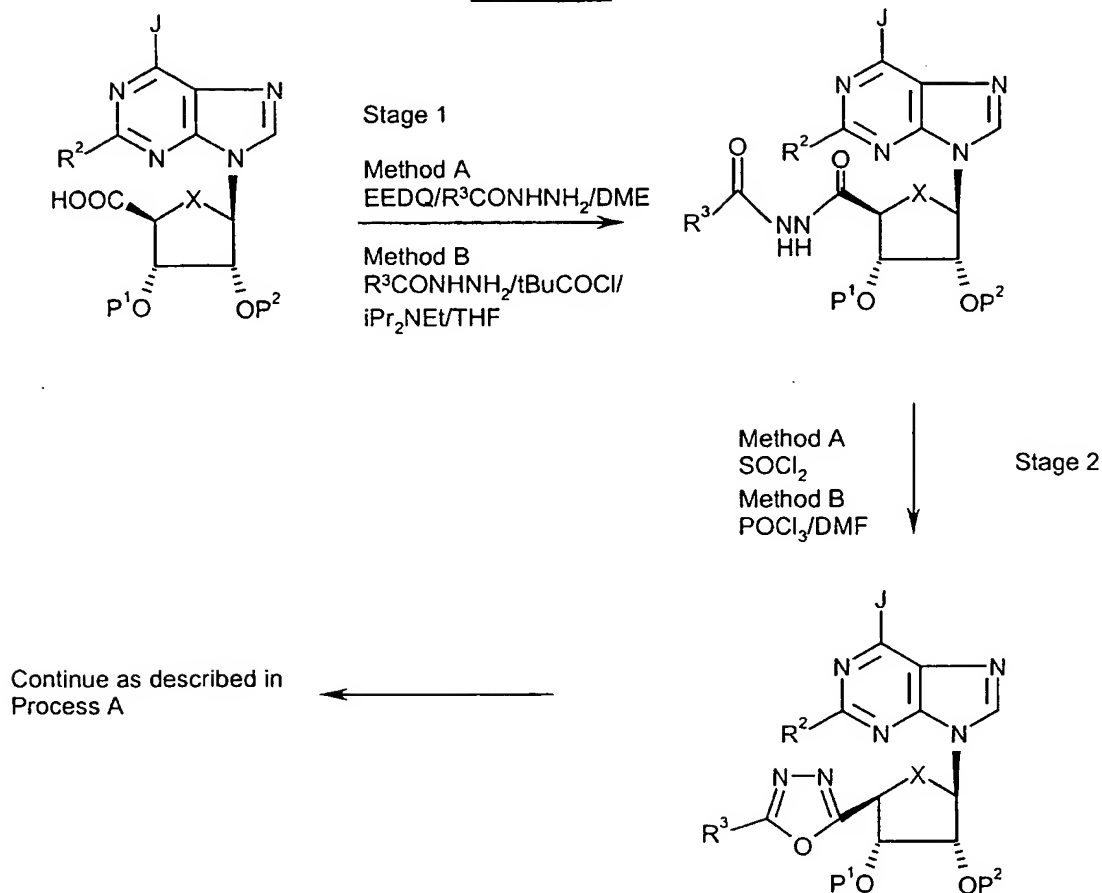


where R<sup>1</sup>, R<sup>2</sup>, X, L, P<sup>1</sup> and P<sup>2</sup> represent groups as previously defined.

Also compounds of formula (VI) may be prepared from compounds of formula (V) by analogous methods to those described in process (A) above.

Synthesis of the compounds of formulae (I) from the corresponding acids of formulae (V) and (VI) will be apparent to a skilled person using conventional synthetic techniques.

As an example, when W = O, Y = N and Z = N in formula 1 above thus defining a 1,3,4 oxadiazole, the synthesis is according to reaction scheme 3. J represents a leaving group L as previously defined, or a NHR<sup>1</sup> group. R<sup>2</sup>, X, P<sup>1</sup> and P<sup>2</sup> are as previously defined.

**Scheme 3**

- Compounds of formula (I) where Z=O, Y=N and W=N (thus defining a 1,3,4-oxadiazole) may be prepared from compounds of formula (V) or (VI) by a first process involving activation of the carboxyl group on the compound of formula (V) or (VI) followed by reaction with an amidoxime of formula HO-N=C(R<sup>3</sup>)NH<sub>2</sub> in a solvent such as tetrahydrofuran or chloroform, in the presence of a base such as pyridine or di-isopropylethylamine, followed by cyclisation at a temperature of 20°C-150°C in a solvent such as toluene, tetrahydrofuran (THF) or chloroform.
- Methods of carboxyl activation include reaction with an acid chloride, such as pivaloyl chloride, or an acid anhydride in the presence of a base such as a tertiary amine, for example di-isopropylethylamine, or with thionyl chloride in dimethylformamide (DMF). Activating agents used in peptide chemistry such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) or 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide

hydrochloride, may also be used. Hydroxyl protecting groups may be removed under conditions known to those practising in the art. For example, the acetonide group may be removed by treatment with an acid (at a temperature of 0°C-150°C) such as trifluoroacetic acid suitably at 0-20°C or acetic acid suitably at 50-150°C.

A preferred compound is (2S, 3S, 4R, 5R)-2-(5-tert-butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluoro-phenylamino)purin-9-yl]tetrahydro-furan-3,4-diol.

Therefore in a preferred aspect of the invention there is provided a method of treating conditions associated with pain and alleviating the symptoms associated therewith which comprises administering to a mammal, including man, (2S, 3S, 4R, 5R)-2-(5-tert-butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluoro-phenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol or a pharmaceutically acceptable derivative thereof and an NSAID, e.g. a COX-2 inhibitor, or a pharmaceutically acceptable derivative thereof.

Suitable NSAIDS for use according to the invention include: naproxen, fenbufen, fenoprofen, flurbiprofen, ketoprofen, dexketoprofen, tiaprofenic acid, azapropazone, diclofenac aceclofenac, diflunisal, indomethacin, ketorolac, mefenamic acid, nabumetone, phenylbutazone, piroxicam, sulindac, tenoxicam, tolfenamic acid, oxaprozin, ibuprofen and COX-2 selective inhibiting compounds (herein referred to as "COX-2 inhibitors").

It will be appreciated that the present invention relates to the use of an adenosine A1 agonist particularly in conjunction with any compound having COX-2 inhibitor activity known in the art.

A variety of COX-2 inhibitors have been described in the art, for example those mentioned in the following patent applications:

|            |           |           |           |           |
|------------|-----------|-----------|-----------|-----------|
| AU9719132  | CA2164559 | CA2180624 | EP-799823 | EP-846689 |
| EP-863134  | FR2751966 | GB2283745 | GB2319772 | GB2320715 |
| JP08157361 | US5510368 | US5681842 | US5686460 | US5776967 |
| US5783597  | US5824699 | US5830911 | US5859036 | US5869524 |



|            |            |            |            |            |
|------------|------------|------------|------------|------------|
| WO94/13635 | WO94/20480 | WO94/26731 | WO95/00501 | WO952/1817 |
| WO96/03385 | WO96/03387 | WO96/06840 | WO96/09293 | WO96/09304 |
| WO96/13483 | WO96/16934 | WO96/19462 | WO96/19463 | WO96/19469 |
| WO96/21667 | WO96/23786 | WO96/24584 | WO96/24585 | WO96/25405 |
| WO96/26921 | WO96/31509 | WO96/36617 | WO96/36623 | WO96/37467 |
| WO96/37469 | WO96/38418 | WO96/38442 | WO96/40143 | WO97/03953 |
| WO97/09977 | WO97/13755 | WO97/13767 | WO97/14691 | WO97/16435 |
| WO97/25045 | WO97/25046 | WO97/25047 | WO97/25048 | WO97/27181 |
| WO97/28120 | WO97/28121 | WO97/30030 | WO97/34882 | WO97/36863 |
| WO97/37984 | WO97/38986 | WO97/40012 | WO97/46524 | WO97/46532 |
| WO98/03484 | WO98/04527 | WO98/06708 | WO98/06715 | WO98/07425 |
| WO98/11080 | WO98/15528 | WO98/21195 | WO98/22442 | WO98/28292 |
| WO98/29382 | WO98/41511 | WO98/41516 | WO98/43966 | WO98/45294 |
| WO98/46594 | WO98/46611 | WO98/47890 | WO98/51667 | WO98/57924 |
| WO99/01455 | WO99/05104 | WO99/10331 | WO99/10332 | WO99/11605 |
| WO99/12930 | WO99/14194 | WO99/14195 | WO99/14205 | WO99/15505 |
| ZA9704806  | ZA9802828  |            |            |            |

all incorporated herein by reference. The above applications also describe, in relation to the COX-2 inhibitors they disclose, both suitable methods for their preparation and doses for their administration.

Suitable COX-2 inhibitors for use according to the invention include: 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine, CDC-501, celecoxib, COX-189, 4-(2-oxo-3-phenyl-2,3-dihydrooxazol-4-yl)benzenesulfonamide, CS-179, CS-502, D-1367, darbufelone, DFP, DRF-4367, etodolac, flosulide, JTE-522 (4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluorobenzenesulfonamide), L-745337, L-768277, L-776967, L-783003, L-791456, L-804600, meloxicam, MK663 (etoricoxib), nimesulide, NS-398, parecoxib, 1-Methylsulfonyl-4-(1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl)benzene, 4-(1,5-Dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)-(2)-benzothiopyran o(4,3-c)pyrazol-1-yl)benzenesulfonamide, 4,4-dimethyl-2-phenyl-3-(4-methylsulfonyl)phenyl)cyclobutenone, 4-Amino-N-(4-(2-fluoro-5-trifluoromethyl)-thiazol-2-yl)-benzene sulfonamide, 1-(7-tert-butyl-2,3-dihydro-3,3-dimethyl-5-benzo-furanyl)-4-cyclopropyl butan-1-one, Pharmaprojects

No.6089 (Kotobuki Pharmaceutical), rofecoxib, RS-113472, RWJ-63556, S-2474, S-33516, SC-299, SC-5755, valdecoxib, UR-8877, UR-8813, UR-8880.

Further suitable COX-2 inhibitors for use according to the invention include: celecoxib, rofecoxib, valdecoxib, parecoxib, 4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluorobenzenesulfonamide (JTE-522), MK663, nimesulide, flosulide, DFP and 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine, and their physiologically acceptable salts or solvates.

Preferred COX-2 inhibitors for use according to the invention are celecoxib, rofecoxib, valdecoxib, parecoxib, 4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluorobenzenesulfonamide (JTE-522) and 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine, and their physiologically acceptable salts or solvates.

A particularly preferred COX-2 inhibitor for use according to the invention is 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine and its physiologically acceptable salts or solvates. Particularly interesting as pharmaceutically acceptable derivatives are modified at the benzenesulphonamide function to provide metabolically labile benzenesulphonamides. Acylated benzenesulphonamide derivatives are of especial interest.

Therefore according to a further aspect of the invention there is provided a method of treating conditions associated with pain and alleviating the symptoms associated therewith which comprises administering to a mammal, including man an adenosine A1 agonist or a pharmaceutically acceptable derivative thereof and celecoxib, rofecoxib, valdecoxib, parecoxib, 4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluorobenzenesulfonamide (JTE-522) and 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine, or a pharmaceutically acceptable derivative thereof.

A particular preferred combination of the invention is (2S, 3S, 4R, 5R)-2-(5 tert-butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluoro-phenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol or a pharmaceutically acceptable derivative thereof and

2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine or a pharmaceutically acceptable derivative thereof.

5 Compounds for use according to the invention may be administered simultaneously or sequentially and, when administration is sequential, either the adenosine A1 agonist or the NSAID, e.g. COX-2 inhibitor, may be administered first. When administration is simultaneous, the combination may be administered either in the same or different pharmaceutical composition.

10 Compounds for use according to the invention may be administered as the raw material but the active ingredients are preferably provided in the form or pharmaceutical formulations.

15 The active ingredients may be used either as separate formulations or as a single combined formulation. When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. Therefore, pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier comprise a further aspect of the invention. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

25 Accordingly in a further aspect of the invention we provide a pharmaceutical composition which comprises a adenosine A1 agonist or a pharmaceutically acceptable derivative thereof and an NSAID, e.g. a COX-2 inhibitor, or a pharmaceutically acceptable derivative thereof formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients.

35 The formulations include those suitable for oral, parenteral (including subcutaneous e.g. by injection or by depot tablet, intradermal, intrathecal, intramuscular e.g. by depot and intravenous), rectal and topical (including

dermal, buccal and sublingual) or in a form suitable for administration by inhalation or insufflation administration, although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the compounds ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation. Preferably such compositions will be formulated for oral administration. It will be appreciated that when the two active ingredients are administered independently, each may be administered by different means.

Formulations suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets (e.g. chewable tablets in particular for paediatric administration) each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a other conventional excipients such as binding agents, (for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, polyvinylpyrrolidone) or hydroxymethyl cellulose or hydroxymethyl cellulose fillers (for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol), lubricants (for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica), disintegrants (for example, potato starch or sodium starch glycollate) or wetting agents, such as sodium lauryl sulfate. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and

may be formulated so as to provide slow or controlled release of the active ingredient therein. The tablets may be coated according to methods well-known in the art.

- 5 Alternatively, the compounds of the present invention may be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, for example. Moreover, formulations containing these compounds may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain
- 10 conventional additives such as suspending agents such as sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum stearate gel or hydrogenated edible fats; emulsifying agents such as lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils) such as almond oil, fractionated coconut oil, oily esters,
- 15 propylene glycol or ethyl alcohol; and preservatives such as methyl or propyl p-hydroxybenzoates or sorbic acid. Such preparations may also be formulated as suppositories, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.
- 20 Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.
- 25 The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of a sterile liquid carrier, for example, water-for-injection, immediately prior to use. Extemporaneous
- 30 injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter, hard fat or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

5

For topical administration to the epidermis, the compounds may be formulated as creams, gels, ointments or lotions or as a transdermal patch.

10 The compounds may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

15

For intranasal administration the compounds of the invention may be used, for example as a liquid spray, as a powder or in the form of drops.

20 For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. 1,1,1,2-trifluoroethane (HFA 134A) and 1,1,1,2,3,3,3, - heptapropane (HFA 227), carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage until may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

25

30 In addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

35 It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or

symptoms. Moreover, it will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general, however, doses employed for adult human treatment will typically be in the range of 0.02-5000 mg per day, preferably 1-1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day. The formulations according to the invention may contain between 0.1-99% of the active ingredient, conveniently from 30-95% for tablets and capsules and 3-50% for liquid preparations.

Pharmaceutical compositions according to the invention may be prepared by conventional techniques. When combined in the same formulation for example, the adenosine A1 agonist or a pharmaceutically acceptable derivative thereof and NSAID, e.g. COX-2 inhibitor, or a pharmaceutically acceptable derivative thereof may be admixed together, if desired, with suitable excipients. Tablets may be prepared, for example, by direct compression of such a mixture. Capsules may be prepared, for example by filling the blend together with suitable excipients into gelatin capsules, using a suitable filling machine.

Compositions for use according to the invention may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredients. The pack may, for example, comprise metal or plastic foil, such as a blister pack. Where the compounds are intended for administration as two separate compositions these may be presented, for example, in the form of a twin pack.

Pharmaceutical compositions may also be prescribed to the patient in "patient packs" containing the whole course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in traditional prescriptions. The inclusion of a

package insert has been shown to improve patient compliance with the physicians instructions.

5 It will be understood that the administration of the combination of the invention by means of a single patient pack, or patients packs of each composition, including a package insert directing the patient to the correct use of the invention is a desirable additional feature of this invention.

10 According to a further aspect of the invention there is provided a patient pack comprising at least one active ingredient, of the combination according to the invention and an information insert containing directions on the use of the combination of the invention.

15 According to another aspect the invention provides a double pack comprising in association for separate administration an adenosine A1 agonist or pharmaceutically acceptable derivative thereof and an NSAID, e.g. COX-2 inhibitor, or pharmaceutically acceptable derivative thereof.

20 It will be appreciated that the dose at which the adenosine A1 agonist and the COX-2 inhibitor is administered will depend on the age and condition of the patient and the frequency and route of administration and will be at the ultimate discretion of the attendant physician. The active ingredients may conveniently be presented in unit dose form.

25 A proposed dose of adenosine A1 agonist and NSAID, e.g. COX-2 inhibitor, for administration to man (of approximately 70kg body weight) may conveniently be administered at doses within the normal range taught in the art at which the compounds are therapeutically effective.

30 For example, a proposed dose of the adenosine A1 agonist for use according to the invention is 0.1mg to 2g, preferably 1mg to 2g, more preferably 1mg to 100mg per unit dose, expressed as the weight of free base. The unit dose may be administered in single or divided doses, for example, from 1 to 4 times per day.



For example, a proposed dose of the NSAID, e.g. COX-2 inhibitor, for use according to the invention is 0.001 to 500mg, preferably 0.01 to 100mg, most preferably 0.05 to 50mg, for example 0.5 to 25mg per unit dose, expressed as the weight of the free base. The unit dose may be administered in single or divided doses, for example, from 1 to 4 times per day.

### **Example 1**

#### **Intermediate 1**

(3aS,4S,6R,6aR)-6-(6-Chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid N'-(2,2-dimethyl-propionyl)-hydrazide

(3aS,4S,6R,6aR)-6-(6-Chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid (2.5g) suspended in 1,2-dimethoxymethane (100ml) was treated with 2,2-dimethyl-propionic acid hydrazide (1.1g) and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), and the mixture heated under reflux for 16h. The mixture was poured into aqueous citric acid (250ml) and extracted with ethyl acetate; the organic layers were washed with citric acid and brine, dried (MgSO<sub>4</sub>) and evaporated in vacuo to give the crude product. Purification by flash chromatography on silica gel (Biotage cartridge), eluting with ethyl acetate:cyclohexane 65:35, gave the title compound as a white solid (1.92g).

LC/MS (System B): R<sub>t</sub> 2.49 min

Mass spectrum *m/z* 439 [MH<sup>+</sup>].

#### **Intermediate 2**

9-[6S-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-6-chloro-9H-purine

(3aS,4S,6R,6aR)-6-(6-Chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid N'-(2,2-dimethyl-propionyl)-hydrazide (1.5g) was dissolved in thionyl chloride (15ml) and the solution irradiated in a microwave oven at 150W power for 7 min. The excess thionyl chloride was evaporated in vacuo to give the crude product which was dissolved in dry acetonitrile (6ml) and heated under reflux for 3h. The solvent was evaporated and the residue purified

by flash chromatography on silica gel, eluting with ethyl acetate:cyclohexane 35:65 – 40:60, to give the title compound as a white solid (0.645g).

LC/MS (System B):  $R_t$  2.86min

5 Mass spectrum  $m/z$  421 [ $MH^+$ ].

### Intermediate 3

9-[(3aR,4R,6S,6aR)-6-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-2,2-  
10 dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]-N-(4-chloro-2-fluorophenyl)-9H-  
purin-6-amine

9-[6S-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-2,2-dimethyl-tetrahydro-(3aR,6aS)-  
furo[3,4-d][1,3]dioxol-4R-yl]-6-chloro-9H-purine (2.8g) was treated with 4-chloro-  
2-fluoro-aniline (4.48ml), palladium acetate (146mg) and (R)-2,2'-  
15 bis(diphenylphosphino)-1,1'-binaphthyl (620mg) in dry toluene (34ml) and the  
mixture stirred at room temperature for 5 mins (reaction carried out in seven  
portions). Caesium carbonate (3.08g, in seven portions) was added, and the  
mixtures heated at 86-96° C for 16h. The mixtures were combined and  
partitioned between water (200ml) and dichloromethane (3x120ml). The organic  
20 layers were washed with brine, dried ( $MgSO_4$ ) and evaporated *in vacuo* to give a  
brown oil (8.7g). Purification by chromatography on silica gel, eluting with ethyl  
acetate:cyclohexane 30:70 gave an off-white solid (2.35g).

LC/MS (System C)  $R_t$  = 3.41 min

25 Mass Spectrum  $m/z$  530 [ $MH^+$ ]

(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluoro-  
phenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol

9-[(3aR,4R,6S,6aR)-6-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-2,2-  
dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]-N-(4-chloro-2-fluorophenyl)-9H-  
purin-6-amine (2.35g) was dissolved in trifluoroacetic acid (20ml) and water  
(2ml) with ice bath cooling, and the mixture allowed to stand at 4°C for 17h. The  
mixture was poured slowly into ice cold saturated aqueous sodium bicarbonate  
35 (400ml) and extracted with ethyl acetate (3x200ml). The organic layers were

washed with brine, dried ( $\text{MgSO}_4$ ) and evaporated *in vacuo* to give the title compound as a buff solid (2.30g).

LC/MS (System C)  $R_t = 3.04$  min.

Mass Spectrum  $m/z$  490 [ $\text{MH}^+$ ]

5

## Example 2

(a) Carrageenan model for (2S, 3S, 4R, 5R)-2-(5 tert-butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluoro-phenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol

10 (Adenosine A1 agonist) and nabumetone (NSAID)

Compound A = (2S, 3S, 4R, 5R)-2-(5 tert-butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluoro-phenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol (Adenosine A1 agonist)

15

### Method:

Male Random Hooded rats (180-220g) were used. The test compound or vehicle was administered 30mins before the 2nd test compound or vehicle. The test compound and vehicles used were: (i) Compound A in 1% DMSO, 66% Peg400, 33% distilled water and (ii) nabumetone in 1% DMSO, 66% Peg400, 33% distilled water. Both test compounds were administered via the oral route. After a further 30mins 100ul of 2% carrageenan was injected intraplantar into the left hind paw and the animals were then returned to their cages. Three hours later behavioural testing of the carrageenan-induced decrease in weight on the inflamed left hind paw (% weight on the inflamed left paw) and associated oedema was assessed. Weight bearing was measured using the dual channel weight averager and paw oedema was assessed using a plethysmometer. The dual channel weight averager is commercially available and is described in the following abstract: Validation of the dual channel weight averager as an instrument for the measurement of inflammatory pain, N.M. Clayton et al., 1997 British Journal Pharmacol. 120, 219P

35

Results:

Table (A) shows the % weight bearing on inflamed paw for (i) the vehicle alone (control), (ii) nabumetone, (iii) Compound A, and (iv) nabumetone and Compound A. Note: In the absence of pain, weight on the hind paws would be evenly distributed, i.e. 50% on each hind paw.

Table (B) shows % inhibition of carrageenan-induced oedema and allodynia, i.e. effect of the drug compared to the control (vehicle only) for (i) nabumetone, (ii) Compound A, and (iii) Compound A and nabumetone. Note: Oedema is the presence of abnormally large amounts of fluid in the intercellular tissue spaces of the body and in the present example is used to provide a measure of inflammation (or anti-oedemic). Allodynia is a sensation of pain resulting from a non-injurious stimulus such as normal heat, cold or pressure on skin and in the present example the weight-bearing (allodynia) effect is used to provide a measure of analgesia.

(A)

| % Weight  | Control    | Nabumetone<br>3mg/kg | Compound A<br>0.4 mg/kg | Nabumetone<br>3mg/kg and<br>Compound A<br>0.4 mg/kg |
|-----------|------------|----------------------|-------------------------|---|
| Allodynia | 20.3 ± 4.3 | 21.6 ± 3.6           | 25.4 ± 2.9              | 35.0 ± 4.8  |

(B)

| %<br>Inhibition | Nabumetone<br>3mg/kg | Compound A<br>0.4 mg/kg | Nabumetone<br>3mg/kg and<br>Compound A<br>0.4 mg/kg |
|-----------------|----------------------|-------------------------|---|
| Allodynia       | 4.3 ± 12.2           | 17.0 ± 9.6              | 49.6 ± 16.1   |
| Oedema          | -25.1 ± 4.7          | -7.4 ± 5.7              | 11.6 ± 6.4  |

The data indicated that (2S, 3S, 4R, 5R)-2-(5 tert-butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluoro-phenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol (Adenosine A1 agonist) dosed in combination with nabumetone (NSAID) produced a more than additive inhibition of the carrageenan-induced decrease in weight bearing on the inflamed left hind paw. This effect may be synergistic.

(b) Carrageenan model for (2S, 3S, 4R, 5R)-2-(5 tert-butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluoro-phenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol (Adenosine A1 agonist) and 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine (COX-2 inhibitor)

Compound A = (2S, 3S, 4R, 5R)-2-(5 tert-butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluoro-phenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol (Adenosine A1 agonist)

Compound B = 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine

The methodology was as described for (a) above. The test compounds and vehicles used were: (i) Compound A in 1% DMSO, 66% Peg400, 33% distilled water and (ii) Compound B in 1% DMSO, 66% Peg400, 33% distilled water. Both compounds were administered via the oral route.

#### Results:

Table (C) shows % inhibition of carrageenan-induced oedema and allodynia, i.e. effect of the drug compared to the control (vehicle only) for (i) Compound B, (ii) Compound A, and (iii) Compound A and Compound B.

(C)

| % Inhibition | Compound B<br>3mg/kg | Compound A<br>0.4 mg/kg | Compound B<br>3mg/kg and<br>Compound A<br>0.4 mg/kg |
|--------------|----------------------|-------------------------|---|
|              |                      |                         |   |

|           |                |                 |                 |
|-----------|----------------|-----------------|-----------------|
| Allodynia | $45.4 \pm 8.9$ | $47.9 \pm 11.1$ | $101.0 \pm 5.6$ |
| Oedema    | $35.8 \pm 3.6$ | $24.9 \pm 5.5$  | $49.9 \pm 5.0$  |

- 5 The data indicated that 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine (COX-2 inhibitor) dosed with (2S, 3S, 4R, 5R)-2-(5 tert-butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluoro-phenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol (Adenosine A1 agonist) shows evidence of at least an additive effect if not synergy between the two compounds in carrageenan.

**Claims**

1. A method of treating conditions associated with pain and alleviating the symptoms associated therewith which comprises administering to a mammal, including man, an adenosine A1 agonist or a pharmaceutically acceptable derivative thereof and an NSAID or a pharmaceutically acceptable derivative thereof.
2. A method according to claim 1 wherein the NSAID is naproxen, fenbufen, fenoprofen, flurbiprofen, ketoprofen, dexketoprofen, tiaprofenic acid, azapropazone, diclofenac aceclofenac, diflunisal, indomethacin, ketorolac, mefenamic acid, nabumetone, phenylbutazone, piroxicam, sulindac, tenoxicam, tolfenamic acid, oxaprozin, ibuprofen, or a COX-2 inhibitor.
3. A method according to claim 2 wherein the NSAID is a COX-2 inhibitor.
4. A method according to any one of claims 1-3 wherein the adenosine A1 agonist is selected from adenosine, N-(4-chloro-2-fluoro-phenyl)-5'-O'-trifluoromethyl-adenosine, N-[1S, trans)-2-hydroxycyclopentyl]adenosine and (2S, 3S, 4R, 5R)-2-(5 tert-butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol, or a pharmaceutically acceptable derivative thereof.
5. A method according to claim 4 wherein the adenosine A1 agonist is (2S, 3S, 4R, 5R)-2-(5 tert-butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol or a pharmaceutically acceptable derivative thereof.
6. A method according to any one of claims 3-5 wherein the COX-2 inhibitor is: 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine, CDC-501, celecoxib, COX-189, 4-(2-oxo-3-phenyl-2,3-dihydrooxazol-4-yl)benzenesulfonamide, CS-179, CS-502, D-1367, darbufelone, DFP, DRF-4367, etodolac, flosulide, JTE-522 (4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluorobenzenesulfonamide), L-745337, L-768277, L-776967, L-783003, L-791456, L-804600, meloxicam, MK663 (etoricoxib), nimesulide, NS-398,

parecoxib, 1-Methylsulfonyl-4-(1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl)benzene, 4-(1,5-Dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)-(2)-benzothiopyran o(4,3-c)pyrazol-1-yl)benzenesulfonamide, 4,4-dimethyl-2-phenyl-3-(4-methylsulfonyl)phenyl)cyclobutenone, 4-Amino-N-(4-(2-fluoro-5-trifluoromethyl)-thiazol-2-yl)-benzene sulfonamide, 1-(7-tert-butyl-2,3-dihydro-3,3-dimethyl-5-benzo-furanyl)-4-cyclopropyl butan-1-one, Pharmaprojects No.6089 (Kotobuki Pharmaceutical), rofecoxib, RS-113472, RWJ-63556, S-2474, S-33516, SC-299, SC-5755, valdecoxib, UR-8877, UR-8813, UR-8880 or a pharmaceutically acceptable derivative thereof.

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7. A method according to any one of claims 3-6 wherein the COX-2 inhibitor is celecoxib, rofecoxib, valdecoxib, parecoxib, 4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluorobenzenesulfonamide (JTE-522) and 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine, or a pharmaceutically acceptable derivative thereof.

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8. A method according to claim 7 wherein the COX-2 inhibitor is 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine, or a pharmaceutically acceptable derivative thereof.

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9. A method according to claim 3 wherein the adenosine A1 agonist is (2S, 3S, 4R, 5R)-2-(5-tert-butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol and the COX-2 inhibitor is 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine, or a pharmaceutically acceptable derivative thereof.

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10. A pharmaceutical composition which comprises an adenosine A1 agonist or a pharmaceutically acceptable derivative thereof and an NSAID or a pharmaceutically acceptable derivative thereof.

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11. A pharmaceutical composition as claimed in claim 10 wherein the NSAID is a COX-2 inhibitor.

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12. A pharmaceutical composition according to claims 10 or 11 adapted for oral administration.



13. A patient pack comprising an adenosine A1 agonist or a pharmaceutically acceptable derivative thereof and an NSAID or a pharmaceutically acceptable derivative thereof.
- 5     14. A patient pack as claimed in claim 13 wherein the NSAID is a COX-2 inhibitor.